Remarks

This Reply is being submitted in compliance with the requirements of 37 C.F.R. § 1.114(c). In accordance with section 706.07(h)II of the MPEP, "a 'submission' includes but is not limited to. . . . new argument. . . ." Applicants respectfully submit that new arguments are being submitted in this reply and therefore the reply meets the criteria to be a submission.

Reconsideration and allowance of this Application is respectfully requested. Claims 1, 8, 10-12 and 42 are pending in the application, with claims 1 and 42 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

In the Advisory Action, at page 2, the Examiner stated that the Reply filed by Applicants on March 17, 2004 did not overcome the rejection under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. Applicants disagree, incorporate by reference herein, reiterate and expand on the Reply filed March 17, 2004.

The Examiner alleges that the term "biological activity substantially similar to the biological activity of parathyroid hormone" is not clear and that the skilled artisan would not be apprised of the metes and bounds of the functional limitation with regard to the function of the encoded polypeptide. Applicants respectfully disagree. The biological activity of parathyroid hormone has been studied extensively, and a person of ordinary skill in the art

would have a clear understanding of what the term "biological activity substantially similar to the biological activity of parathyroid hormone" encompasses. Indeed, the information disclosure statement submitted in the above-captioned application references numerous publications that discuss the biological activity of parathyroid hormone and the assays available to test such activity. As discussed in the Applicants' previous replies, the specification itself also provides ample guidance as to what the biological activity of parathyroid hormone is and how it can be measured.

The Examiner states that "[s]ince detailed information regarding the structural and functional requirements of the encoded polypeptide is lacking, it is thus unpredictable as to which variations, if any, meet the limitations of the claims." Applicants respectfully point out that claim 1 claims polypeptides having substitutions at four of its 14 positions. Moreover, there are at most only three allowed amino acids per substituted position. Therefore, Applicants fail to understand the Examiner's assertion that the structural requirements are not well defined.

Applicants note that they are not required to provide experimental examples of each and every polypeptide that would fall under the scope of the claims. *See, e.g., Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1237, quoting *In re Angstadt,* 537 F.2d 498, 502, 190 U.S.P.Q. (BNA) 214, 218 (CCPA 1976) ("it is not necessary that a patent applicant test all the embodiments of his invention. . . . what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims."). Applicants respectfully draw the Examiner's attention to multiple examples of muteins and fragments that have led Applicants to the claimed invention. For example, the Examiner is urged to review Example 2, Table 2; Example 6, Table 3; Example 7, Table 4; and Figures 1-7, in which the biological activity of several muteins and fragments

of a polypeptide, having a one or more of the mutations that transform native rPTH(1-14) to a polypeptide of SEQ ID NO:1, is measured in different experimental systems. Furthermore, Applicants have tested many muteins and mapped the positions that tolerate substitution. Applicants have provided ample guidance as to the structural features that enable a mutein or variant to maintain activity by elucidating the substitution-tolerant positions in the peptide (*see, e.g.,* pages 64-71). Moreover, Applicants explicitly disclose the biological activity and the testing for such biological activity of $[A^{3},A^{10},R^{11},A^{12},W^{14}]$rPTH(1-14)amide, a polypeptide of SEQ ID NO. 1. If after reviewing the examples the Examiner still maintains the rejection, he is respectfully requested to state with specificity why the examples are insufficient to overcome the rejection.

Applicants also respectfully draw the Examiner's attention to pages 64-71 in which experiments testing the *activity* of muteins with single and multiple amino acid substitutions are described. Moreover, the tests to measure the function of the claimed muteins are also described in detail in the specification. In view of the foregoing discussion, applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph for lack of enablement be withdrawn. Alternatively, Applicants respectfully request that the Examiner explain the alleged insufficiency of the examples discussed above. In the absence of such explanation, the rejection cannot stand.

In the Advisory Action, the Examiner also stated that the March 17, 2003 Reply does not overcome the rejection under 35 U.S.C. § 112, first paragraph, as lacking written description. The Examiner again alleges that the term "biological activity substantially similar to the biological activity of parathyroid hormone" is not clear and that the skilled artisan would not be apprised of the metes and bounds of the functional limitation with regard to the function of the encoded polypeptide. Applicants respectfully disagree. As discussed

above, the biological activity of parathyroid hormone has been studied extensively, and a person of ordinary skill in the art would have a clear understanding of what the term "biological activity substantially similar to the biological activity of parathyroid hormone" encompasses, as evidenced by the numerous publications cited by Applicants in the information disclosure statement.

The Examiner alleges that the specification "fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of encoded polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed." Applicants respectfully disagree. As discussed above, 10 out of the 14 residues in the claimed polypeptides are constant, *i.e.*, a common primary structure of the molecule. Applicants respectfully request a clarification as to why such common primary structure is insufficient to be a common structural element shared by all the members of the claimed genus.

The Examiner also states that "[t]here is no description of the sites at which variability may be tolerated. . . ." Applicants respectfully disagree. As discussed above, Applicants have designated only four residues as tolerant of substitution and, at most, only three amino acid variants per position. Thus, Applicants respectfully assert that the Examiner is wrong.

Furthermore, as the Examiner himself acknowledges, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice. On page 73, Applicants state that $[A^{3},A^{10},R^{11},A^{12},W^{14}]$rPTH(1-14)amide, a peptide of the claimed genus, was 220-fold more potent than native PTH(1-14). Thus, it is apparent from the specification that the invention was reduced to practice.

Moreover, Applicants tested over 100 peptides in which individual native amino acids in the native rPTH(1-14) were substituted with other amino acids (see Figure 1). In addition, Applicants tested peptides in which two, three or four of the substitutions according to SEQ ID NO: 1 were combined. Thus, the inventors mapped out the positions that were amenable to substitution and the combinations of substitutions that produced active peptides. Furthermore, the claimed peptides contain conserved substitutions. For example, the permitted amino acids at position 14 are Trp or Phe, both of which are aromatic, and both of which resulted in higher activity than the native His when substituted in the native polypeptide (see Figure 1). Therefore, even though experiments in which each and every claimed peptide may not be described in the specification, the results of assaying $[A^{3},A^{10},R^{11},A^{12},W^{14}]$rPTH(1-14)amide, in addition to the results of assaying the other peptides, provide ample evidence that the inventors were in possession of the invention at the time of filing the above-captioned application.

In view of these arguments, applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, for lack of written description, be withdrawn. Alternatively, Applicants respectfully request that the Examiner address the specific facts laid out above, and explain why the examples in the specification are not sufficient to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants

believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Lawrence B. Bugaisky

Lawrence B. Bugaisky
Attorney for Applicants
Registration No. 36,203

Date: April 19, 2004

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

253261_1.DOC